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Hepatitis B

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Some HBV Genotypes Have Naturally-Occurring Resistance to Antiviral Drugs

Historically, researchers have assumed that naturally-occurring hepatitis B virus (HBV) had no inherent, built-in resistance to antiviral medications. They thought it took months or years of antiviral use for HBV to develop resistance to the drug.

However, researchers in Argentina have identified cases where patients with HBV strains or genotypes E and F appeared to have inherent resistance to certain antivirals,

according to their report published in the April 2010 issue of the journal of *Antiviral Resistance*.

Antiviral medications make it difficult for HBV to reproduce by meddling with their replication process. Researchers assumed drug resistance to these antivirals occurred over a long period of time as the antiviral killed off the naturally-occurring HBV. The few HBV with mutations that could “resist” and reproduce despite antiviral treatment would slowly increase in number over time and the infection would rebound as the number of resistant HBV increased.

The researchers in Argentina followed 13 chronically-infected patients with natural antiviral resistance to at least one antiviral drug. Five of them also had a mutation in the hepatitis B surface antigen (HBsAg), the protein that makes up the covering of the virus. As a result of these mutations, the patients had naturally-occurring resistance to the antiviral adefovir (Hepsera).

These findings suggest that doctors may want to examine a patient’s HBV for mutations before starting antiviral therapy, the researchers suggest, “in order to choose the proper (antiviral) for optimizing the thera-

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peutic management of chronically infected patients.” The researchers also noted that the naturally occurring drug-resistant HBV, “should be of public health concern as they may represent an additional risk for the community.”

Researchers Discover Why Men with HBV Have Higher Liver Cancer Rates than Women

A team of Taiwanese and U.S. researchers have discovered that androgen receptors—which play a role in the body’s production of testosterone—are the reason why HBV-infected men are seven-times more likely to develop liver cancer than women.

The androgen receptor appears to facilitate development of liver cancer in two ways, according to the report published in the May 20th issue of *Science Translational Medicine*. First, the receptor

appears to enable HBV viral replication, which results in higher HBV DNA levels in the bloodstream that increase the risk of liver cancer. Second, the androgen receptor appears to promote the development of tumors in the liver.

To examine the role of the androgen receptor, researchers used transgenic technology to create the first mouse in the world genetically modified to lack androgen receptor in its liver cells. Earlier experiments showed that simply decreasing the concentration of androgen in the bloodstream could not effectively treat liver cancer, so the scientists focused on removing androgen specifically from liver cells.

In the experiment, the team injected low doses of the carcinogen diethylnitrosamine into normal mice and mice that were infected with HBV 16 days after they were born. By week 22, only mice in-

fectured with HBV had developed liver tumors.

They repeated the experiment, this time using the transgenic mice that lacked androgen receptors in their liver cells as well as normal mice. Both groups were infected with HBV and then injected with the carcinogen.

By week 22, the normal mice were six times more likely to develop liver tumors than the transgenic mice.

The results present researchers with a new approach to treating liver cancer—by specifically targeting the androgen receptors in liver cells.

Interferon-Telbivudine Treatment Combination Effective, But Increases Risk of Peripheral Neuropathy

An international team of researchers, presenting their findings at the 45th European Association for the

Study of the Liver conference, treated 110 hepatitis B e antigen (HBeAg)-positive patients with the antiviral telbivudine (Tyzeka) alone, pegylated interferon alone, or a combination of the two to see if the combination would be more effective in increasing the rate of HBeAg seroconversion (loss of HBeAg and development of “e” antibodies) than the single drug treatments.

After 24 weeks of treatment, the combination treatment achieved a significantly greater decline in the amount of HBV circulating in patients’ bloodstreams (called viral load or HBV DNA) than the individual treatments.

HBV DNA became undetectable in 35% of telbivudine-only treated patients, 7% of interferon-treated patients, and 71% of patients treated with the telbivudine-interferon combination. The drop in HBsAg and HBeAg was also

greatest in patients receiving combination treatment.

However, the combination treatment resulted in a higher rate of patients experiencing peripheral neuropathy (PN)—nerve damage that causes numbness and pain in hands and feet. Those receiving combination treatments developed these symptoms within four weeks, compared to those receiving only telbivudine, who developed symptoms on average after 14 weeks of treatment.

The researchers recommended avoiding this combination treatment, despite its increased effectiveness.

Indefinite Antiviral Treatment Appears Necessary, Even after HBeAg Seroconversion

Dutch researchers explored the long-term durability of HBeAg seroconversion during antiviral treatment in 132 HBeAg-positive patients who were treated for two

years.

HBeAg seroconversion occurred in 46 of 132 patients (35%).

Forty-two of the 46 patients were followed for 59 months after seroconversion, and 13 (31%) demonstrated a durable remission, defined as being HBeAg-negative with undetectable viral load, but it lasted for only a limited time period. Overall:

- Researchers reported that 33 of the 42 (79%) continued therapy after HBeAg seroconversion; of these, 22 (67%) had a recurrence of elevated viral load and infection.
- Nine of the 42 (21%) eventually discontinued therapy after HBeAg seroconversion. Only 2 patients demonstrated a durable response in the absence of therapy.
- A resurgence in viral load and liver damage recurred in 80%

of patients who were taking lamivudine (Epivir-HBV) due to the development of drug resistance.

Long-term continuation of antiviral treatment, even when HBeAg seroconversion occurs, appears to be necessary, researchers wrote in the April 2010 issue of *Gastroenterology*.

Medically-Supervised Heroin “Consumption Rooms” Could Reduce Crime and Bloodborne Infections

Researchers made the case for creating medically-supervised “consumption rooms” that would provide heroin to injecting drug addicts as a way to reduce crime, drug addiction, and transmission of blood-borne infections such as HIV, HBV, and hepatitis C, during a presentation at the Royal College of Nursing’s annual conference.

This practice, of-

officials argued, would enable Britain’s National Health Service to cut the transmission of blood-borne viruses like HIV and viral hepatitis and provide a “stepping stone” to wean users off heroin and onto methadone with the help of counseling and health care.

Medically-supervised consumption rooms in Sydney, Australia, and Amsterdam have resulted in fewer addicts injecting in public places.

Pilot studies at King’s College’s national addiction center suggest medically-supervised injection sites could cut local crime rates by two-thirds over six months. Of 127 pilot participants, 75% substantially reduced their use of street drugs. The number of crimes they committed declined from 1,731 in three months to 547 in six months.

The participants had access to a range of support services, including

counseling, and typically attended the clinic up to two times a day, seven days a week. The annual cost per patient was about \$22,965, compared with the expense of incarcerating prisoners, which costs about \$61,240 a year.

San Francisco Has the Highest Rate of Liver Cancer in U.S. Due to Hepatitis B Prevalence

Recent data released by the National Cancer Institute confirms that San Francisco has the highest rate of liver cancer in the nation. It is the gateway for immigrants arriving from Asian countries where the prevalence of chronic hepatitis B can exceed 10%.

An estimated one in 10 Asian-American immigrants is chronically infected with HBV, compared to 1 in 1,000 in the general population. HBV infection causes up to 80% of liver cancers

worldwide.

There are more than 43,000 new hepatitis B cases in United States each year, with the greatest incidence among adults between ages 19-49 years old.

Combination Lamivudine and Interferon Appears Effective Against HBV Exacerbations

Japanese researchers treated 12 patients who were experiencing an acute exacerbation of their chronic HBV infection, signaled by increased alanine aminotransferase (ALT) levels, which indicate liver cell damage or death, and a surge in viral load.

The patients, nine of whom were HBeAg-positive, were treated with lamivudine 100 mg/day alone for 20 weeks, then with both lamivudine and conventional interferon three times per week and lamivudine for four weeks, and lastly, with interferon alone for 20 weeks.

Four of the nine (44.4%) HBeAg-positive and all three HBeAg-negative patients achieved normal ALT levels and undetectable viral load. Three of four patients (75%) who lost HBeAg at the end of treatment achieved a sustained response (undetectable viral load and normal ALT levels), while one of five (20%) whose HBeAg remained positive achieved a sustained response.

The researchers, writing in the April 2010 issue of the journal of *Hepatology Research*, concluded that this sequential therapy, “enables the withdrawal of treatment and is particularly effective for patients whose HBeAg has become undetectable by the end of the interferon treatment.”

Fewer HBV-Infected Transplant Patients Are Requiring a Second Transplant

The number of HBV-infected liver transplant patients

who require a second transplant within three years decreased by 50% between 1996 and 2005, according to a Mayo Clinic report presented at the American Transplant Congress in early May.

The improvement in post-transplant health is due to use of hepatitis B immune globulin (HBIG—hepatitis B antibodies) and antivirals to prevent re-infection, according to researchers.

Researchers reviewed data provided by the Organ Procurement and Transplantation Network of 31,242 liver transplants in the United States. Hepatitis B- and C-related liver disease were among the leading causes. Between 1996 and 1998, 6.5 percent of liver transplant patients with hepatitis B were listed for a second transplant. Between 2003 and 2005, that number declined to 3.3 percent.

However, over the same time periods, the death rate for

hepatitis B transplant patients increased from 10.8 percent from 1996 to 1998, to 12.8 percent from 2003 to 2005. While researchers were happy with the decline in second liver transplants request, there is growing concern about the increase in mortality rates, possibly due to untreated hepatitis B that results in untreatable liver cancer. Currently in the United States, about 16,000 people are waiting for liver transplants.

Early Detection Increases Liver Cancer Survival Among Asian-Americans

Researchers at the Dumont-University of California, Los Angeles, Liver Cancer Center followed 278 Asian-Americans treated for liver cancer over a seven-year period to assess what impact treatment had on survival.

The average age of patients on enrollment was 61.5, and 68% of the

Chinese-, Korean-, and Vietnamese-American patients in the study group were HBV-infected, whereas 60% of Japanese patients had hepatitis C.

Compared with patients who presented with symptoms, patients referred for cancer treatment who had been diagnosed through regular screening tended to have more tumors.

Using UCLA treatment guidelines, 83% of patients received treatment, and those receiving orthotopic liver transplantation and radiofrequency ablation had the highest overall patient survival rate. Those receiving orthotopic liver transplantation had the highest disease-free survival rates.

Researchers, writing in the *Journal of Clinical Gastroenterology*, noted that HBV and HCV were associated with more than 90% of liver cancer cases in Asian-Americans. Additionally, liver can-

cer detected by regular screening identified more patients who were eligible for surgical and locoregional therapies, which improved overall and disease-free survival.

More Than Half of Liver Patients Have Neurocognitive Impairments

More than half of patients who have cirrhosis also have neurocognitive impairments, such as short-term memory loss, according to by Loyola University Health System medical researchers published in the the May 3 *Digestive Disease Week*.

Researchers reported that 54% of 301 cirrhosis patients who were tested scored below the 10th percentile for their age and education on a test that measures neurocognitive abilities, which can affect working, driving, and managing personal finances.

Neurocognitive impairment in liver

patients is called hepatic encephalopathy. It is believed to be caused by toxins such as ammonia that diseased and scarred livers are not able to clear from the body.

Liver patients from multiple centers nationwide were given a test developed by Randolph called the Repeatable Battery for the Assessment of Neuro-psychological Status (RBANS™). In the general population, the average score on the test is 100. Among liver patients who had neurocognitive impairments, the average score was 74. This is lower than the average score of patients with early-stage Alzheimer's disease.

Researchers are now studying whether an experimental compound called AST-120, which absorbs ammonia and other toxins, would benefit liver patients who have neurocognitive impairments.

Nail Problems Higher in Patients with Liver Damage

An examination of hepatitis B patients' nails may now be included as part of a regular medical exam of hepatitis B patients, based on findings by European researchers, published in the June 2010 issue of the *Journal of the European Academy of Dermatology & Venereology*.

They compared the nails of 100 patients infected with HCV and HBV and others who had other liver diseases, with the nails of 100 healthy people.

Nail changes were identified in 68% of the patient group, compared to 35% of the control group. The nail infection onychomycosis was the most common finding in 18% of liver disease patients, compared to 10% of the control group, followed by longitudinal striations, brittle nails, onychorrhexis, clubbing of

fingers, dystrophic nails, leukonychia and longitudinal melanonychia.

Nail changes are observed in patients with liver cirrhosis, and with those infected with HCV and HBV, researchers noted. "...This will add additional clinical criteria for general practitioners and dermatologists to help them with diagnosis of these common systemic infections," they wrote.

Only 20% of Cirrhotic Patients Are Properly Screened for Liver Cancer

Fewer than 20% of patients with cirrhosis (severe scarring of the liver) who develop liver cancer were regularly screened for cancer before their cancer detection, according to a study by U.S. researchers, published in a recent issue of *Hepatology*.

Current clinical guidelines recommend that cirrhotic

patients receive regular screening through an alpha fetoprotein (AFP) test, a blood test that indicates the presence of tumors, and an ultrasound.

Researchers studied 1,873 patients age 65 and older who developed liver cancer and were previously diagnosed with cirrhosis between 1994 and 2002.

In the three years before their liver cancer diagnosis, 17% regularly received the prescribed surveillance for cancer and 38% received inconsistent surveillance. In a subset of 541 patients in whom cirrhosis was recorded for three or more years prior to their cancer diagnosis, only 29% received routine surveillance and 33% received inconsistent surveillance.

Among all patients who received regular surveillance, approximately 52% received both AFP and ultrasound, 46% received AFP only, and 2% re-

ceived ultrasound only. Patients receiving regular surveillance were more likely to have lived in urban areas and had higher incomes than those who did not receive surveillance.

Those patients seen by gastroenterologists or hepatologists, who specialize in treating liver diseases, were approximately 4.5-fold more likely to receive regular surveillance than patients seen only by a primary care physician.

